a reduction in GEF activity, rather than an increase. This unexpected result is at odds with a simple picture of a direct tradeoff between cAMP binding energy and ionic lock release. DIMS trajectories of the conformational transition allow us to compute the energetic role of the mutation in entropy-enthalpy compensation and elucidate the allosteric communication pathways that are modulated by the mutation. Reference trajectories of the wild-type and the mutation (R886A) in the inactive and active states give us additional insights into the nature of the changes.

2298-Pos Board B68

Distinguishing Features of Aquaglyceroporin in Plasmodium Falciparum: Comparative Molecular Dynamics Simulations of Three Aquaporins

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Aquaporins help to maintain water homeostasis and diverse members have been identified across all three kingdoms of life (http://bioinfo.iitk.ac.in/MIPModDB). These remarkable channel proteins facilitate the transport of water and other neutral solutes across biomembranes. Their selectivity has been attributed to two constrictions within the channel namely aromatic/arginine selectivity filter (SF) and the conserved NPA motif. Despite the wealth of data available from experimental and computational studies, the physical basis of selectivity is still not completely understood. A recent structure of an aquaporin (PfAQP) from the malarial parasite *Plasmodium facliparum,* which is also a potential drug target for malaria,was found to possess SF identical to a glycerol-specific aquaglyceroporin (GlpF). Interestingly, it was observed that PfAQP transports both water and glycerol equally efficiently.

The molecular basis of dual specificity in PfAQP continues to puzzle researchers. Although the overall fold is same, one of the distinguishing features could be distinct non-covalent interactions specific to only PfAQP. In order to find out any such interaction, we have carried out MD simulations of PfAQP and compared with water-selective AQP1 and glycerol-specific GlpF in explicit lipid bilayer. RMSD analysis shows that AQP1 is the most flexible channel protein. The more rigid PfAQP and GlpF are characterized by the presence of additional salt-bridge and cation-π interactions. Moreover, certain loops have stronger interactions with transmembrane helices in both PfAQP and GlpF. To further enhance our understanding we performed three additional simulations by creating *in-silico* mutants in GlpF and AQP1 that either disrupted the existing interactions or resulted in new interactions. The results from these simulations clearly demonstrated the important role of certain non-covalent interactions in solute transport and hints that aquaporin channel transport can be regulated in multiple ways.

2299-Pos Board B69

Exploring the Mechanism and Functional (A)Symmetry of ATP Binding Cassette Domains

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RNase-L Inhibitor, also known as ABCE1, is an ATP Binding Cassette (ABC) protein which contains only the two nucleotide binding domains (NBDs) and an iron sulfur (FeS) cluster. It was suggested to be associated with various aspects of protein synthesis, including the binding of translation initiation factors, translation release factors, export of ribosomal subunits from the nucleus and ribosome recycling. ABCE1 had been resolved by X-ray in its ADP-bound conformation only. The two NBDs possess a high structural similarity between themselves despite that they do not share the same sequence (33% identity only). Moreover, despite this structural symmetry, ABCE1 has been reported to be functionally asymmetric, where mutations in one NBD (E238Q, H269A) reduce its ATP hydrolysis by 30-50% of normal wild type activity, while the parallel mutations in the second NBD increase it by a 10-fold. Our study aims revealing the reason for this phenomena, while shedding light on the structure and mechanism of action of ABC domains. In the study presented, we differentiate ABC domains' structure according to different modes of nucleotide binding (ATP bound, ADP bound, and nucleotide free). We present the main global collective motions that occur upon the conformational change between those binding modes, and based on that, we derive an atomistic model for the closed (ATP-bound) conformation. Based on these atomistic models of the ATP and ADP bound conformations, nucleotide affinity and cooperativity effects which may influence that affinity are examined, with the goal to understand the source of the detected functional asymmetry.

2300-Pos Board B70

Molecular Dynamics Simulation of Interaction of a Cytotoxin with a Lipid Bilayer: A Multiscale Modeling

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The interaction of cytotoxins, small three fingered proteins, with lipid bilayers as cell's membranes has many important biological effects in nature and may lead to deform or in some cases rupture of lipid bilayers. In this work the interaction of a cardiotoxin (CTXA3) from cobra snake venom with a 1-Palmitoyl-2-Oleoylphosphatidylcholine (POPC) lipid bilayer has been studied. All atom molecular dynamics simulation is used to simulate the system and to reveal the binding mode of CTXA3 with lipid membrane. The results show the binding mode of CTXA3 POPC lipid membrane. According to the binding mode, the coarse grained model of the system has been constructed in order to calculate the pressure distribution in the system. The pressure profiles of systems with and without protein have been compared. The effect of insertion of protein in the bilayer on pressure profile has been studied.

2301-Pos Board B71

Improving the Performance of Constant pH Molecular Dynamics with Generalized Born Electrostatics

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Conventional molecular dynamics (MD) simulations require that protonation states for all acidic and basic residues are fixed for the duration of the simulation. The conformational space sampled in the simulation is thus biased by the input protonation states, and the interplay between protonation change and conformational change is lost. Constant pH molecular dynamics (CpHMD) methods allow protonation states of titratable residues to change during the MD simulation, allowing for coupling between protonation and conformational to occur. Herein, we present a CpHMD method with generalized Born (GB) electrostatics, employing Monte Carlo steps within the simulation to allow protonation states to change discretely over the course of the simulation. Learning from pKa blind predictions conducted on the Staphylococcus nuclease Δ+PHS variant, our work focuses on improving the sampling of protonation space through alterations to the Monte Carlo scheme. Improvements to this method will enable better descriptions of pH-dependent phenomena in computer simulations, including ligand binding and protein folding.

2302-Pos Board B72

The Copper-Release Pathway of the CopA ATPase

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P-type ATPases belonging to class IB maintain heavy metal homeostasis by means of ion extrusion across cell membranes. The first crystal structure of the class, a copper-transporting ATPase (CopA), provided clues to their transport mechanism. Six invariable residues were situated in a transmembrane (TM) cluster, representing two disordered high-affinity ion binding sites. Moreover, two flanking groups of residues consisting of methionines and negatively charged side-chains were suggested to represent transient intracellular entry and extracellular exit sites, respectively, although the entry-to-internal- sites distance would necessitate large conformational changes to allow copper transfer. Free copper ions are rare in cells and therefore the pathway was proposed to be initiated by the docking of a copper-binding structural entity, likely a chaperone, to an IB-specific platform in the vicinity of the entry site. To monitor protein dynamics in a lipid environment, we performed molecular dynamics (MD) simulations of CopA inserted into a dioleoylphosphocholine (DOPC) bilayer. The platform was found to expose three positively charged amino acids to the water environment, thereby providing the required antenna for docking with the negatively charged chaperones. Furthermore, the significant side-chain flexibility observed for entry-site Met148 would facilitate copper transfer by reducing the distance to the internal sites. Unexpectedly, solvation effects indicated the position of two internal binding sites. Moreover, a water exit pathway, imposed by the dynamical TM helix MA, connected the putative exit site at Glu189 with the extracellular space, indicating a class-specific transport mechanism.